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Towards treating progressive Multiple Sclerosis

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Few neurological conditions have seen such a rapid increase in treatment options as Multiple Sclerosis (MS) and that trajectory continues to the present day. However, it is also the case that this increase in treatments is in the early more inflammatory relapsing forms of the condition. The great challenge to the MS field is to develop truly effective treatments which target neurodegeneration (or neuro-axonal loss), which is thought to be responsible for clinical progression. Implicit within the challenge of treating progressive MS, is a better understanding of the clinical phenotypes which can only come from a deeper understanding of underlying mechanisms – an essential prerequisite in the identification of new treatment targets.

Understanding mechanisms of progression

A critical step towards the discovery of treatments for patients with MS is to understand the biological dynamics that lead to the progressive phase of MS.[1] Inflammation remains an important element, but it is different from that seen in relapsing MS, since it is characterised by the presence of inflammation (mainly CD8+ T and CD20+ B lymphocytes) within the parenchyma, compartmentalized behind a (partly) closed or repaired blood–brain barrier,[2] and chronic active and/or slowly expanding lesions,[3] which show a preferential accumulation of resident microglia with M1 differentiation (associated with inflammatory and degenerative processes) at the lesion edge.[4] In addition, in progressive MS there seems to be a failure in repair mechanisms, including inability of senescent oligodendrocytes progenitor cells to differentiate and surviving oligodendrocytes to myelinate.[1]

When moving from a microstructural level to a macrostructural one, an abnormal communication between brain regions (or connectivity),[5] linked to degeneration of the long-range connections,[6] may contribute to cognitive dysfunction in MS. Furthermore, an exhaustion of brain reserve may lead to, or exacerbate, functional deficits in MS.[7]

The identification of new targets, which play a critical role in progression, is one of key drivers behind the establishment of international networks by the Progressive MS Alliance. A recent example of the work funded by the Alliance is the identification of epigenetic modifiers as candidate targets to suppress the pathogenic activity of astrocytes in MS.[8]

Predicting progression

Imaging biomarkers are providing greater insights into progression and, importantly, helping to identify patients who more likely to progress. Established MRI measures, available in routine clinical practice, including brain gadolinium enhancing and spinal cord lesions, are predictors of very long-term disease outcomes. [9] Promising candidates, which are not routinely obtained in clinical practice, include slowly expanding lesions[10] and tissue loss, notably infratentorial and spinal cord atrophy.[11] Atrophy of specific grey matter regions,[12] especially thalamic atrophy,[13] has a particularly strong association with clinical progression. There is also clear evidence of faster cortical atrophy in progressive MS, which is associated with cognitive decline.[14]

Optical coherence tomography, which allows acquisition of high-resolution images of various retinal layers, has demonstrated retinal thinning in progressive MS exceeding relapsing MS. Importantly, it has been suggested in a large retrospective cohort study that OCT may predict disability progression in individual patients.[15]

Other than imaging biomarkers, the emergence of the serum neurofilament light has been greeted with great enthusiasm, although it still requires validation. Although not specific for MS, it may have potential to identify patients who will enter the progressive phase and in whom progression may increase with greater rapidity.[16]

Improved descriptors of progressive phenotypes

There has been a recent effort to clarify the descriptors of the progressive phenotypes (primary progressive and secondary progressive MS) and, in particular, clarity around the timeframe and use of the terms activity, progression and worsening, which had been causing considerable confusion,

not least in relation to indications for specific agents, as outlined by the EMA and FDA.[17] Importantly, it is recommended to reserve the term progressing or disease progression to describe patients in a progressive phase of MS who are accruing disability, independent of any relapse activity; progression should be evaluated annually.[17]

Therapeutic trials of disease modifying treatments

Turning to therapeutic trials of progressive MS, there have been a few successes which have helped to offset the disappointment of earlier negative studies of agents, such as fingolimod and natalizumab. The first of these was the positive Phase III trial of ocrelizumab in primary progressive MS,[18] which was followed shortly afterwards by positive study of siponimod in secondary progressive MS.[19] These agents have a modest therapeutic benefit, with up to 25% slowing of progression – perhaps reflecting their mode of action. In the US, siponimod has been supplemented by the FDA's ruling that all agents that have an effect on relapsing MS should have their indication extended to include secondary progressive MS with evidence of activity. Evidence of activity is defined as having clinical relapses and does not include new MRI activity. This has meant that agents, such as cladribine, may now be used in the US for patients with secondary progressive MS, who continue to have relapses, but only if they have failed other treatments.

Another strategy for identifying effective treatments in progressive MS is drug repurposing (also called drug repositioning, reprofiling or re-tasking) which aims to find new uses for approved or investigational drugs that are outside the scope of the original medical indication. Examples of drug repurposing in MS which have shown an effect in reducing brain atrophy in secondary progressive MS are simvastatin,[20] which is now studied in a Phase III trial, and ibudilast,[21] whose investigators are now looking for sponsor for a Phase III trial. The approach of combining drug repurposing and innovative trial design is particularly attractive, because of reduced time-frame for drug development and costs saving. An example of this approach is the MS-SMART trial which incorporated three repurposed agents (amiloride, fluoxetine and riluzole), and while proving that the multi-arm design was feasible and efficient, it was emphatically negative.[22]

To have a truly effective impact on progression, it is likely that neuroprotective and repair mechanisms will need to be targeted. In relation to remyelination/repair, this continues to be a very challenging area though an active field of research as investigators strive to improve.[23] Promising agents are currently being studied (Figure 1), but the number is low and there is a real need for further focus on this area.

Improving symptomatic management

We should not forget the need to improve both rehabilitation and symptomatic management in MS – and particularly in progressive MS. There has been a major focus on the benefits of exercise not only on motor function and progression, but also potentially on cognitive function. This has culminated in a major international study, led from Canada and sponsored by the Canadian MS Society, which will evaluate in considerable detail the impact of aerobic exercise on cognitive function.[24] Another encouraging recent study, which assessed a home-based standing frame programme in progressive MS, showed a significant improvement in motor function and quality of life.[25] Beyond the clinical efficacy of the intervention, this trial is important because it showed that such studies are feasible and can demonstrate cost effectiveness.

Conclusion

As is often the case, reflecting over the last few years, is both encouraging and stimulating. However, the challenge of understanding the mechanisms underpinning progression remains, and until we really understand what progression actually means, we will struggle to develop truly effective treatments. That has to be the main focus for the next five years, hopefully driven and enabled by organisations such as the Progressive MS Alliance.

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Figure 1: **Agents that are currently being studied in progressive MS treatments**.

Figure Footnote:
In orange, treatments whose development pipeline is led by industry. The FDA has ruled that all agents that have an effect on relapsing MS (which are the first 10 treatments on the list) should have their indication extended to include secondary progressive MS with evidence of activity. Biotin was tested in a placebo-controlled Phase III trial, but in March of this year it was announced that the trial had failed to meet its primary and secondary endpoints, and, therefore, it is marked with an X. (*Courtesy of Timothy Coetzee, Tim Coetzee, National MS Society*).

Competing interests

OC has served on Scientific Advisory Boards and has received honoraria and support for travel from Novartis, Roche, Merck; is deputy editor for Neurology and serves on the Editorial Board for Multiple Sclerosis Journal; receives research support from EPSRC, NIHR, MS Society of GB and NI, National MS Society, Rosetrees Trust, and the NIHR UCLH/UCL Biomedical Research Centre.

AJT has served on Scientific Advisory Boards and received honoraria from Eisai and Abbvie; has received support for travel from the International Progressive MS Alliance as chair of their Scientific Steering Committee, and from the National MS Society as a member of their Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief of Multiple Sclerosis Journal, and is an editorial board member for the Lancet Neurology; receives research support from NIHR and the NIHR UCLH Biomedical Research Centre.